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(54) Title: ULCER PREVENTION AND TREATMENT COMPOSITION AND METHOD		
(57) Abstract		
<p>Anti-ulcer compositions are disclosed having therapeutic agents dispersed in a soluble matrix formed by melt spinning the therapeutic agent with a carrier and hydrogel. Methods of treating ulcer-bearing tissue and preparing the matrix are also disclosed. One embodiment includes use of gastric irritating bio-affecting agents in which case the composition is preventative as well as therapeutic.</p>		

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ULCER PREVENTION AND TREATMENT COMPOSITION AND METHODBACKGROUND OF THE INVENTION

5 This is a Continuation-in-Part application of co-pending
U.S. application Serial No. 808,599 which was filed on December
17, 1991.

10 The present invention relates to ulcer treatments. In
particular, the present invention relates to the use of dosage
forms containing anti-ulcer agents dispersed in a soluble
matrix.

15 Sucralfate is a therapeutic compound useful for treatment
of various gastrointestinal disorders. Sucralfate accelerates
the healing of gastric and duodenal ulcers and also finds use
as a symptomatic treatment for disturbances such as dyspepsia
and reflux.

20 Sucralfate displays its action in the acid medium of the
digestive tract where it lines ulcerated mucous membranes of
the stomach and duodenum with a protective coating. The
preferential binding affinity of sucralfate for ulcerated areas
of mucous membrane results in increased protection and
accelerated healing of ulcers as well as regeneration of the
mucous membrane.

25 Although sucralfate is usually taken orally in the form of
tablets, other dosage forms are known. For example, U.S.
Patent No. 4,885,281 discloses an aqueous suspension containing
sucralfate, xanthum gum and a "peptiser". Peptisers such as
salts of inorganic or organic acids are added to ensure that
the xanthan gum does not separate out of the suspension by gel
formation.

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Belgium Patent No. 900,605 discloses a composition of sucralfate and a nonsteroidal anti-inflammatory product. The compositions were prepared for administering to mammalian test specimens by suspending the active substances in an aqueous medium containing 0.5% sodium CMC (carboxymethylcellulose).

The preparation of melt-spun medicament-containing products is known. For example, commonly-assigned U.S. Patent No. 4,855,326, which is incorporated by reference herein, discloses combining a medicament with a melt-spinnable carrier agent, preferably a mixture of sucrose and lactose, and then melt-spinning the mixture to form a spun product.

Similarly, commonly-assigned U.S. Patent No. 4,997,856, also incorporated by reference herein, discloses melt spun, compacted dispersible systems containing a medicament, saccharide and an oleaginous substance such as a food oil.

In keeping with foregoing, improvements are continuously being sought using high shear and/or heat processing to enhance the delivery of medicaments. In the case of anti-ulcer medicaments such as sucralfate, investigation is being conducted to improve the protective and therapeutic action of the medicament on ulcerated areas of mucous membranes.

It is an object of the present invention to provide an improved method of treatment using medicaments spun in a matrix carrier.

It is a further object of the present invention to provide improved methods and compositions for preventing and treating ulcerated mucosa.

Other and further objects will become apparent to the artisan in view of the present disclosure, and the scope of the present application is not to be limited by the objects set forth above.

SUMMARY OF THE INVENTION

The present invention includes anti-ulcer compositions formed by having a medicament dispersed in a soluble matrix. The soluble matrix is formed by subjecting the feedstock to physical and/or chemical changes associated with flash flow processing, such as by melt-spinning the medicament with a mixture of a carrier material and a hydrogel. The anti-ulcer compositions can either be placed directly on the ulcer-bearing tissue/mucosa or may be dispersed in a liquid before contacting the affected tissue.

The medicament included in the composition of the present invention is preferably sucralfate. Alternatively, H₂-blocking agents such as cimetidine and the like or omeprazole may also be included.

The carrier materials included in the mixture are a saccharide-based and preferably materials such as maltodextrin, maltooligosaccharides or polydextrose. The hydrogel is selected from materials such as xanthan gum, guar gum and carrageenan. In a preferred embodiment, the melt spinning mixture also includes an oleaginous substance such as a vegetable oil. A method of preparing such anti-ulcer compositions is also disclosed.

The composition of the present invention can also include an analgesic and non-steroidal anti-inflammatory (NSAI) agent. The non-steroidal anti-inflammatory agent may be selected from the various classes of such compounds, e.g., salicylates, acetic acids, propionic acids, fenamates, oxicams, and oxidoles. A processing aid, such as glycerin, can be used in manufacture of the composition.

The composition of the present invention can also include steroids or other gastric irritating drugs. The steroids may be Andrenocorticoids such as Betamethasone, Cortisone,

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Dexamethasone, Hydrocortisone, Methylprednisolone, Paramethasone, Prednisolone, Prednisone, Triamcinolone or Corticotropins and the like. Examples of steroids include, but are not limited to, medicaments set forth by trade name as follows: Aristocort - Lederle; Hydrocortone - Merck Sharp & Dohme; Kenalog (in Orabase) - Squibb; Cortone - Merck Sharp & Dohme; Decadron - Merck Sharp & Dohme; and Medrol - Upjohn.

In yet another embodiment an antacid can be included in the composition. The antacid can be incorporated in the feedstock before being processed under flash-flow condition, or, alternatively, it can be separately processed under flash-flow condition and combined in a delivery system. For example, the antacid can be processed separately to form flakes which can then be combined with flakes bearing anti-ulcer medicament and optionally analgesic, by tableting the flakes together in a single tablet.

The present invention also includes a method of treating ulcer-bearing tissue. The method includes contacting the affected tissue with an anti-ulcer medicament dispersed in a soluble matrix as set forth above. Preferably, the medicament-containing matrix has been dispersed in a liquid such as water before contacting the ulcer-bearing tissue.

As a result of the present invention, anti-ulcer compositions are provided which present therapeutic agents in a rapidly soluble form. In addition, since the therapeutic agents are melt spun with a hydrogel in addition to a soluble carrier, the composition demonstrates mucosal adherence properties and enhanced mouthfeel due to the thickening effect of the hydrogel. These added features provide an enhanced therapeutic effect as well by rapidly placing the anti-ulcer medicament in contact with the affected tissue and affixing it there for a period of time. The hydrogel also acts to assist in suspending the medicament during melt spinning within the spun matrix.

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Moreover, when the active agents set forth above are prepared in accordance with the present invention, the product has markedly enhanced tableting capability. This product is ideal for preparing tableted delivery systems such as pills, etc.

Yet another advantage is that the compositions of the present invention provide good coating action for internal tissue surfaces of the body by virtue of its substantially uniform adherence to mucosal tissue.

For a better understanding of the present invention, reference is made to the following description, and its scope will be pointed out in the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The anti-ulcer compositions of the present invention are formed by melt spinning medicaments with a mixture of a carrier material and hydrogel so that the medicament is suspended in a soluble matrix.

When a non-steroidal anti-inflammatory agent is included, sucralfate and the NSAID agents are admixed prior to processing. In a preferred embodiment, the carrier material is also mixed with the active ingredients prior to processing. A processing aid can be used to provide bulk for thorough mixing. Glycerin is useful as a processing aid.

The active ingredients are subjected to flash-flow processing. Flash-flow processing can be accomplished several ways. Flash heat and flash shear are two such processes which can be used. In the flash heat process, the feedstock material is heated sufficiently to create an internal flow condition which permits part of the feedstock to move at a subparticle level with respect to the rest of the mass and exit openings provided in the perimeter of a spinning head. The centrifugal

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force created in the spinning head flings the flowing feedstock material outwardly from the head so that it reforms with a changed structure. The force required to separate and discharge flowable feedstock is centrifugal force which results from the spinning head. The flash heat process is one process for producing the product of this invention.

In the flash shear process, a shearform matrix is formed by raising the temperature of the feedstock material which includes a nonsolublized-carrier to a point where the carrier such as a saccharide-based material undergoes internal flow upon application of a fluid shear force. The feedstock is advanced and ejected while in internal flow condition, and subjected to disruptive fluid shear forces to form multiple parts or masses which have morphology different from that of the original feedstock.

The multiple masses are cooled substantially immediately after contact with the fluid shear force and are permitted to continue in a free-flow condition until solidified.

In the flash heat process, a spinning process is used herein, wherein the medicament is combined with a carrier and is spun with "cotton candy" fabricating type equipment. The floss spinning machine used herein can be any cotton candy type machine, such as the Econofloss Model 3017 manufactured by Gold Metal Products Company of Cincinnati, Ohio. It will be appreciated by those skilled in the art from the present description that any apparatus or physical process which provides similar forces and temperature gradient conditions can also be used. For simplicity in disclosing and describing this invention, the term "melt-spinning" will be understood to mean a process which includes a combination of temperature, shear, flow, flow rate, mechanical forces and thermal gradients of the type utilized in a cotton candy type machine.

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In melt-spinning, the stock material, historically sucrose, is melted and forced through spinnerettes. Conventional equipment includes a rotating spinning head surrounded by a bowl into which the fibers are spun. Typically, the temperature of the grid in the spinning machine required for spinning sucrose is from about 180°F to about 266°F at operating speeds of about 3800 RPM. Other saccharides such as maltodextrins and polydextrose, however, can be spun at temperatures as much as 30 to 40% lower and thus permit many heat-sensitive materials to safely undergo melt spinning. It has also been discovered that the extremely short amount of time the medicaments, saccharides and hydrogels are exposed to the melt spinning temperature and shear allows the inventive matrix to be formed without harm.

The flash shear process can be carried out in an apparatus which has means for increasing the temperature of a non-solubilized feedstock and means for simultaneously advancing it for ejection. A multiple heating zone twin screw extruder can be used for increasing the temperature and advancing feedstock. The second element of the apparatus is a means for ejecting the feedstock in a condition for shearing it to provide the product. The means for ejecting is in fluid communication with the means for increasing the temperature and is arranged at the point to receive the feedstock while it is in the internal flow conditions. The means for ejecting the feedstock is preferably a nozzle which provides high pressure ejection of the feedstock material. For a description of various apparatus which can be used to produce the inventive delivery systems, see copending U.S. Serial No. (Docket 447-65), filed October 23, 1992 entitled "Process for Making Shearform Matrix", which is herein incorporated by reference.

Various anti-ulcer agents, such as H₂-blocking agents may be included in the anti-ulcer composition of the present invention. A non-limiting list of such agents include cimetadine, ranitadine, nizatidine and famotidine.

Alternatively, anti-ulcer agents such as omeprazole may be selected. In a preferred embodiment, however, the anti-ulcer agent is sucralfate. Mixtures of the above-identified medicaments are also contemplated.

5 The anti-ulcer agent will be present in amounts up to 50% by weight and preferably from 0.1 to about 20% by weight of the matrix. Most preferably, however, the medicament is present in amounts of from about 0.5 to about 15% by weight of the matrix. The amount of medicament in the matrix is that amount
10 sufficient to achieve the desired therapeutic result. The optimum dosing of the anti-ulcer medicaments is left with the skill of the artisan.

 The anti-ulcer medicament is melt spun with a mixture of a carrier material and hydrogel. The carrier material is
15 preferably a saccharide-based material. A non-limiting list of suitable saccharides include sucrose, maltose, fructose, glucose and lactose. Alternatively, carrier materials can be selected from maltodextrins, polydextrose, corn syrup solids, maltooligosaccharides and mixtures thereof.

20 The hydrogels included in the melt-spinning mixture are selected from materials such as xanthan gum, guar gum, carrageenan gum, gum tragacanth, similar materials, and mixtures thereof. The hydrogel will be present in an amount of from about 0.2% to about 4% by weight of the matrix, with
25 amounts of from about 0.8 to about 2.5% being preferred.

 Hydrogels, which may also be referred to as water-soluble polymers, hydrocolloids or hydrophilic polymers, demonstrate the property of being able to adhere to mucous membranes. Materials such as pectins, gelatin, celluloses and
30 polycarbophil are also of use. By including such mucous-adhering materials in the matrix, the anti-ulcer medicament can be maintained in contact with the affected area, that is, ulcer-bearing tissue. For example, upon contact with ulcer-

bearing mucosal tissue, the saccharide portion of the matrix quickly dissolves, leaving the medicament and hydrogel adhering to the affected area. Even when the matrix is dispersed in a liquid before administration, adherence of the medicament to mucosal areas is observable. Thus, the therapeutic properties of the medicament can be directed and affixed to the particular area needed.

In a further embodiment of the present invention, the mixture of the carrier material and hydrogel can also include an oleaginous substance which functions to assure that as the matrix is formed during melt spinning, the active ingredient is substantially evenly distributed in the carrier. In this regard, oleaginous substances such as polyvinylpyrrolidone (PVP) or vegetable oils such as corn oil, sunflower oil, olive oil and mixtures thereof may be present in amounts of from about 2 to about 20% by weight of the matrix, with amounts of from about 5 to about 15% being preferred.

The medicament, hydrogel, and carrier material may be combined prior to or during melt spinning. For example, the mixture containing the carrier and hydrogel are first combined into a uniform mixture before adding the medicament and any optionally present materials such as flavors, sweeteners or oleaginous materials.

In one embodiment, the composition can also include a non-steroidal anti-inflammatory (NSAI) agent selected from the various classes of such compounds. Such classes include, for example, salicylates such as acetylsalicylic acid and diflunisal; acetic acids such as indomethacin, sulindac, tolmetin, diclofenac, and etodolac; propionic acids such as flurbiprofen, indoprofen, naproxen, and ketoprofen; fenamates such as meclofenamate; oxicams such as piroxicam; and oxindoles such as tenidap.

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When the composition includes an NSAID agent, the actives are preferably mixed prior to flash-flow processing. The actives can be mixed with a processing aid which can be glycerin, for example.

5 The anti-ulcer composition may also optionally include a flavorant. Flavorants include flavors, sweeteners and combinations thereof. The flavors may be natural, artificial or mixtures thereof while the sweeteners may be natural, artificial or high intensity sweeteners or mixtures thereof.
10 Such flavorant materials can be melt spun with the medicament and carrier/hydrogel mixture so that the flavorant is also dispersed within the spun matrix. The amount of flavorant included in the matrix will be a matter of preference for the artisan. It is anticipated that the flavorant will be present
15 in amounts of from about 0.01 to about 3% by weight of the matrix. In addition, the anti-ulcer compositions prepared in accordance with the present invention may also include materials such as colorants, anti-oxidants, preservatives, and the like.

20 Depending upon the saccharide selected for inclusion in the matrix, the melt-spun medicament product will be in the form of floss, flakes, spicules and the like. In any event, the scope of the present invention is not confined to the physical form of the product, so long as the anti-ulcer
25 medicament is sufficiently dispersed throughout.

 In an alternative embodiment, antacid can also be included. Antacids are any alkaline substance which can be taken internally to neutralize stomach acidity. Substances which can be used as antacid include aluminum hydroxide,
30 calcium carbonate, magnesia and alumina oral suspensions, magnesium oxide, magnesium trisilicate, magaldrate, simethicone, and sodium bicarbonate. Other substances can be used and the scope of the invention is not limited to those substances set forth above.

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The embodiment which includes antacids can be prepared with the antacid combined in the feedstock with the anti-ulcer medicament and/or analgesic before flash-flow processing. However, in yet another alternative, antacid can be flash-flow processed separately and then combined in a delivery system such as a tablet, capsule, powder, etc. For example, when the flash-flow product is a flake, separate anti-ulcer flakes and antacid flakes can be mixed and then tabletted. The resulting tablet carries both actives intimately bound together in a delivery system, yet physically separated to reduce chemical interaction. The practitioner will realize yet other methods for providing the antacid with the anti-ulcer medicament and, optionally, analgesic compounds using the flash-flow process, and it is intended to include these other methods which are within the scope of the present invention.

If desired, the resultant medicament-containing spun matrix can be compacted to less than 15% of the as-spun volume. An example of such compacting methods is set forth in commonly-assigned U.S. Patent No. 4,997,856, the disclosure of which is incorporated herein. In addition, the spun matrix may also be reduced in particle size such as by milling to provide medicament containing either "particles" or "particulate".

A further aspect of the present invention is a method of treating ulcer-bearing tissue. The method includes contacting ulcer-bearing tissue with an anti-ulcer medicament dispersed in a soluble matrix formed by melt-spinning the medicament with a mixture of a carrier material and a hydrogel, such as that set forth above as the anti-ulcer composition.

The medicament containing matrix may be placed in contact with the ulcer-bearing tissue in the as-spun form, as a compacted wafer or after being dispersed in a liquid. In the situations where the matrix is affixed directly to ulcer-bearing tissue, the presence of the hydrogel in the matrix allows the medicament to be affixed at the site of treatment.

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Alternatively, an effective amount of anti-ulcer composition can be dispersed water and, after dissolving, can be taken orally for treatment of mouth or other gastrointestinal mucous-bearing tissue ulcers. The dosages can be varied depending upon the requirements of the patient and the severity of the condition being treated. The actual optimum dosage is within the skill of the artisan.

The compositions of the present invention may also be used as antacid substitutes for palliative relief of dyspepsia, reflux, gastritis and the like. In short, it is anticipated that the medicament-containing spun matrix can be used for any therapeutic indication for which the medicament included in the matrix is suited. Moreover, when the compositions of the present invention include NSAID agents, the unique combination is also preventative in nature.

EXAMPLES

The following examples serve to provide further appreciation of the invention but are not meant in any way to restrict the effective scope of the invention. Unless
5 indicated otherwise, the Econofloss machine referred to above was used to form the flash-flow product.

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EXAMPLE 1
ANTI-ULCER COMPOSITION

<u>INGREDIENTS</u>	<u>WT. (GRAMS)</u>
Sucralfate (Powder)	25.0
5 Xanthan Gum	2.0
Corn Oil	12.5
Peppermint Oil	0.5
Maltodextrin 35R (Corn Syrup Solid)	209.5

10 In this example, a sucralfate-containing anti-ulcer composition was prepared. Initially, the carrier material was prepared by mixing the xanthan gum and maltodextrin until a substantially homogeneous mixture was obtained. Thereafter, the sucralfate, corn oil and peppermint oil flavorant were
15 added while mixing was continued. The resultant mixture was then spun at a low setting. A white spicule-like flake was obtained.

 A one tablespoon quantity of the resulting matrix was added to a glass of tap water at room temperature. After
20 quickly dissolving, a colloidal suspension was formed which had a viscosity thicker than tap water.

 The resultant mixture was ingested by a host having distress from an ulcerated stomach. The inventive composition provided dramatic relief of stomach ulcer pain instantaneously.
25 It appears that the unique combination of ingredients subjected to the high shear and heat processing had a remarkable effect on the speed and the extent of the treatment.

 In the case of treatment of mouth ulcers, one tablespoon of the resulting matrix is added to two tablespoons of tap
30 water to obtain a viscous solution which has excellent coating properties. The viscous solution provides excellent immediate and sustained relief when used for oral cavity ulcers.

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EXAMPLE 2ANTI-ULCER COMPOSITION

<u>INGREDIENTS</u>	<u>WT. (GRAMS)</u>
Sucralfate (Powder)	25.0
5 Xanthan Gum	1.68
Glycerin	11.25
Maltodextrin 35R (Corn Syrup Solid)	212.07

10 In this example, a sucralfate-containing anti-ulcer composition was prepared. Initially, the carrier material was prepared by mixing the xanthan gum, sucralfate and glycerin until a substantillay homogeneous mixture was obtained. Thereafter, the Maltodextrin was added while mixing was continued. The resulting mixture was then spun at a low
15 setting. A white spicule-like flake was obtained.

Three tablespoons of the spun matrix was mixed with six tablespoons of water to make a viscous liquid mixture. The viscous mixture was used as a mouth rinse by a host having severe mouth ulcerations. About one day after using the
20 viscous rinse, the host observed substantially reduced irritaiton of the ulcerated areas, especially when eating food.

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EXAMPLE 3ANTI-ULCER COMPOSITION

	<u>INGREDIENTS</u>	<u>WT. (GRAMS)</u>
	Cimetidine (Powder)	5.0
5	Xanthan Gum	2.0
	Corn Oil	12.5
	Peppermint Oil	0.5
	Maltodextrin 35R (Corn Syrup Solid)	209.5

10 In this example, the process set forth in Example 1 is repeated except that the anti-ulcer agent cimetidine is used. A tablespoon quantity of the resultant spun matrix is added to a glass of water and quickly dissolves forming a somewhat viscous colloidal suspension.

15 The suspension is ingested by a host suffering gastric distress. The medication quickly relieves the stomach pain associated with gastritis and dyspepsia. The viscous suspension is also effective in relieving the discomfort associated with gastrointestinal reflux, since the viscous
20 liquid adheres to the upper portion of the gastric mucosa as well as stomach contents.

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EXAMPLE 4
ANTI-ULCER COMPOSITION

	<u>INGREDIENTS</u>	<u>WT. (GRAMS)</u>
5	Sucralfate (Powder)	25
	Xanthan Gum	2
	Olive Oil	12.5
	Spearmint Oil	0.5
10	Maltodextrin 35R (Corn Syrup Solid)	209.5

In this example, the medicament-containing matrix is prepared as in the Example 1, except that after the matrix is formed, it is compacted to about 15% of its as-spun volume in the form of wafers.

15 The wafers were then placed on ulcer-bearing oral cavity tissue of an affected host without being dissolved in water. Once placed on the ulcer-bearing tissue, the saccharide portion of the matrix quickly dissolves and the hydrogel portion of the composition, xanthan gum, along with the medicament remain
20 affixed to the oral cavity ulcer-bearing tissue to provide instantaneous relief from the discomfort associated with the ulcerated tissue in the oral cavity.

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EXAMPLE 5

In this example, the anti-ulcer medicament sucralfate was mixed with the NSAID agent acetylsalicylic acid. Glycerin was used as a processing aid and the active ingredients mixed by mortar and pestle. Corn syrup solids (D.E. = 36.5), Maltrin-365, was added and mixed well. Xanthan gum was also added to form the feedstock. The ingredients were mixed in the amounts set forth in the Table below.

NSAID PLUS SUCRALFATE/HYDROGEL

<u>Active wt %</u>	<u>CSS DE=36.5 wt %</u>	<u>Aid wt %</u>	<u>Hydrogel wt %</u>
Sucralfate 10%	Maltrin-365 74%	Glycerin 5%	Xanthan Gum 1%
Acetylsalicylic acid 10%			

The feedstock was processed by subjecting the feedstock to flash-flow conditions in a Tornado spinning machine which had been modified to control two parameters: temperature of the heating element, and speed (RPM) of the rotating head. The diameter of the head was 5.5 inches. The feedstock was processed at 3600 RPM and at 135°C.

The resulting product was in the form of flakes which contained a substantially uniform dispersion of the active ingredients. Furthermore, the product had a consistent color and texture, which made it easily adaptable for inclusion in a delivery system such as a tablet.

The above example can also be prepared with ibuprofen as a NSAID agent. The results are a flake which can be easily used in the formation of a delivery means such as a tableted pill or capsule.

EXAMPLES 6 & 7

Corn Syrup Solids (D.E.=36.5) were melt spun in combination with three drugs to produce a flake-like matrix useful in the present invention. Two examples of this composition feature the drug sucralfate as the common active ingredient. In addition to sucralfate, in Example 6 aspirin has been incorporated; and in Example 7, ibuprofen has been incorporated.

Each composition was formed by first mixing the drugs with a processing aid (glycerin) by mortar and pestle. The excipient, corn syrup solid (Maltrin-365), was slowly added and mixed well. The entire admixture was then processed in a Cuisinart until homogeneous.

Both example mixtures were melt-spun with a modified Tornado spinning machine to allow for control of two parameters: temperature of the heating ribbon, and speed (RPM) of the rotating head. The diameter of the head was 5.5 inches.

The Table below indicates the relative weight percents of the melt-spun components as well as the temperature and rotational speed of the spinning head.

NSAI PLUS SUCRALFATE

<u>Example</u>	<u>Drug wt %</u>	<u>CSS DE=36.5 wt %</u>	<u>Aid wt %</u>	<u>RPM</u>	<u>TempC</u>
6	Sucralfate 10% Aspirin 10%	Maltrin-365 75%	Glycerin 5%	3,600	135
7	Sucralfate 10% Ibuprofen 10%	Maltrin-365 75%	Glycerin 5%	3,600	135

Flakes were analyzed for the presence of drugs with a Mattson Galaxy 5020 FTIR against a nitrogen purge background. Samples were compared to the FTIR spectra of the individual ingredients.

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2 grams of each flake example were ground in a SPEX Wig L Bug ball mill. 5 mg resulting powder was added to 400 mg crystalline KBr and ground again in SPEX mill. This material was split in two equal portions to provide duplicate samples for analysis. Pellets were formed in a SPECAC press by exerting 10 tons of pressure for 1 minute.

IR spectrographs of the melt-spun material confirm the presence of sucralfate in both examples. Spectrographs also confirm that Aspirin was present in the processed sample of Example 6, while Ibuprofen was present in the processed sample of Example 7.

Thus, the product resulting from both example 6 and 7 provide both preventative and therapeutic effect at the site of delivery.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize the changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to claim all such changes and modifications as fall within the true scope of the invention.

WHAT IS CLAIMED IS:

1. An anti-ulcer composition comprising an anti-ulcer medicament dispersed in a soluble matrix formed by subjecting to flash-flow conditions said medicament with a mixture of a carrier material and a hydrogel.
2. The composition of Claim 1, wherein said anti-ulcer medicament is sucralfate.
3. The composition of Claim 1, wherein said anti-ulcer medicament is selected from the group consisting of cimetadine, ranitadine, nizatidine, famotidine, omeprazole and mixtures thereof.
4. The composition of Claim 1, wherein said medicament is present in an amount of from about 0.1 to about 50% by weight of said matrix.
5. The composition of Claim 4, wherein said medicament is present in an amount of from about 0.1 to about 20% by weight of said matrix.
6. The composition of Claim 5, wherein said carrier material is a saccharide.
7. The composition of Claim 6, wherein said carrier material is selected from the group consisting of

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maltodextrins, corn syrup solids, polydextrose, maltooligosaccharides and mixtures thereof.

8. The composition of Claim 7, wherein said hydrogel is selected from the group consisting of xanthan gum, guar gum, carrageenan gum, gum tragacanth, sodium alginate, gum karaya, locust bean gum, gum acasia and mixtures thereof.

9. The composition of Claim 8, wherein said hydrogel is present in an amount of from about 0.2 to about 4% by weight of said matrix.

10. The composition of Claim 9, wherein said hydrogel is present in an amount of from about 0.8 to about 2.5% by weight of said matrix.

11. The composition of Claim 1, wherein said mixture further comprises an oleaginous substance.

12. The composition of Claim 11, wherein said oleaginous substance is selected from the group consisting of corn oil, sunflower oil, olive oil, vegetable oils and mixtures thereof.

13. The composition of Claim 12, wherein said oleaginous substance is present in an amount of from about 2 to about 20% by weight of said matrix.

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14. The composition of Claim 13, wherein said oleaginous substance is present in an amount of from about 5 to about 15% by weight of said matrix.

15. The composition of Claim 1 which further comprises a gastric-irritating bio-affecting agent.

16. The composition of Claim 15, wherein said bio-affecting agent is a non-steroidal anti-inflammatory (NSAI) agent.

17. The composition of Claim 16 wherein said NSAI is selected from the groups consisting of salicylate NSAI agents, acetic acid NSAI agents, oxicam NSAI agents, oxidole NSAI agents and mixtures thereof.

18. The composition of Claim 15 wherein said bio-affecting agent is a steroid.

19. The composition of Claim 18 wherein said steroid is selected from the group consisting of adrenocorticoids and corticotropins.

20. The composition of Claim 1 wherein an antacid is included in said matrix by subjecting said antacid to flash-flow along with said medicament and said mixture.

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21. The composition of Claim 20 which further comprises a non-steroidal anti-inflammatory (NSAI) agent subjected to flash-flow with said antacid and said medicament and said mixture.

22. A method of treating ulcer-bearing tissue, comprising contacting ulcer-bearing tissue with an anti-ulcer medicament dispersed in a soluble matrix formed by subjecting to flash-flow conditions said medicament with a mixture of a carrier material and a hydrogel.

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23. The method of Claim 22, wherein said anti-ulcer medicament is sucralfate.

24. The method of Claim 22, wherein said anti-ulcer medicament is selected from the group consisting of cimetadine, ranitadine, nizatidine, famotidine, omeprazole and mixtures thereof.

25. The method of Claim 22, wherein said medicament is present in an amount of from about 0.5 to about 50% by weight of said matrix.

26. The method of Claim 25, wherein said medicament is present in an amount of from about 0.5 to about 20% by weight of said matrix.

27. The method of Claim 26, wherein said carrier material is a saccharide.

28. The method of Claim 27, wherein said carrier material is selected from the group consisting of maltodextrins, corn syrup solids, polydextrose, maltooligosaccharides and mixtures thereof.

29. The method of Claim 28, wherein said hydrogel is selected from the group consisting of xanthan gum, guar gum, carrageenan gum, gum tragacanth, sodium alginate, gum kayara, locust bean gum, gum acasia and mixtures thereof.

30. The method of Claim 29, wherein said hydrogel is present in an amount of from about 0.2 to about 4% by weight of said matrix.

31. The method of Claim 30, wherein said hydrogel is present in an amount of from about 0.8 to about 2.5% by weight of said matrix.

32. The method of Claim 31, wherein said mixture further comprises an oleaginous substance.

33. The method of Claim 32, wherein said oleaginous substance is selected from the group consisting of corn oil, sunflower oil, olive oil, vegetable oils and mixtures thereof.

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34. The method of Claim 33, wherein said oleaginous substance is present in an amount of from about 2 to about 20% by weight of said matrix.

35. The method of Claim 34, wherein said oleaginous substance is present in an amount of from about 5 to about 15% by weight of said matrix.

36. The method of Claim 22 further comprising dispersing said matrix in a liquid before contacting said ulcer-bearing tissue.

37. A method of preparing an anti-ulcer composition having an anti-ulcer medicament dispersed in a soluble matrix comprising:

5 subjecting a feedstock comprising said medicament and a carrier material to flash-flow transformation.

38. The method of Claim 37 wherein said feedstock further comprises a hydrogel.

39. The method of Claim 37 wherein said feedstock further comprises a non-steroidal anti-inflammatory (NSAI) agent.

40. The method of claim 39 wherein said NSAI agent is selected from the groups consisting of salicylate NSAI agents, acetic acid NSAI agents, propionic acid NSAI agents, fenamate

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NSAI agents, oxicam NSAI agents, oxidole NSAI agents and mixtures thereof.

41. The method of Claim 39 wherein said feedstock comprises an admixture of said NSAI agent and said medicament and a processing aid.

42. The method of claim 41 wherein said processing aid is glycerin.

43. The method of Claim 22 which further comprises including an antacid in said soluble matrix by subjecting said antacid to flash-flow conditions with said medicament and said mixture.

44. The method of Claim 43 which further comprises a non-steroidal anti-inflammatory (NSAI) agent.

45. A method of treatment with a non-steroidal anti-inflammatory (NSAI) agent comprising contacting a patient with an NSAI agent and an anti-ulcer medicament dispersed in a soluble matrix formed by subjecting a feedstock comprising
5 carrier material, and said anti-ulcer medicament to flash-flow conditions.

46. The method of Claim 45 wherein said feedstock further comprises a hydrogel.

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47. The method of Claim 45 wherein said anti-ulcer medicament is sucralfate.

48. The method of Claim 45 wherein said anti-ulcer medicament is selected from the group consisting of cimetadine, ranitadine, nizatidine, famotidine, omeprazole and mixtures thereof.

49. The method of claim 45 wherein said medicament is present in an amount from about 0.1 to about 50% by weight of said mixture.

50. The method of Claim 49 wherein said medicament is present in an amount from about 0.5 to about 20% by weight of said mixture.

51. The method of Claim 50 wherein said carrier materials selected from the group consisting of maltodextrins, corn syrup solids, polydextrose, maltooligosaccharides and mixtures thereof.

52. The method of Claim 47 wherein said hydrogel is selected from the group consisting of xanthane gum, guar gum, carrageenan, gum tragacanth, sodium alginate, gum cyara, locust bean gum, gum acacia and mixtures thereof.

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53. The method of Claim 52 wherein said hydrogel is present in an amount from about 0.2 to about 4% by weight of said matrix.

54. The method of Claim 53 wherein said hydrogel is present in an amount from about 0.8 to about 2.5% by weight of said matrix.

55. The method of Claim 54 wherein said mixture further comprises an oleaginous substance.

56. The method of Claim 55 wherein said oleaginous substance is selected from the group consisting of corn oil, sunflower oil, olive oil, vegetable oils and mixtures thereof.

57. The method of claim 56 wherein said oleaginous substance is present in an amount of from about 2 to about 20% by weight of said matrix.

58. The method of claim 57 wherein said oleaginous substance is present in an amount of from about 5 to about 15% by weight of said matrix.

59. The method of claim 45 further comprising dispersing said matrix in a liquid before contacting with said patient.

60. The method of claim 45 wherein said feedstock further comprises a processing aid.

61. The method of Claim 45 wherein said feedstock further comprises an antacid.

62. An anti-ulcer medication comprising:

5 a) an anti-ulcer medicament dispersed in a first matrix formed by subjecting to flash-flow condition a first feedstock comprising said medicament and a mixture of a carrier material and hydrogel;

b) an antacid agent dispersed in a second matrix formed by subjecting flash-flow conditions a second feedstock comprising said antacid and a carrier material.

63. The medication of Claim 62 wherein said first feedstock further comprises a non-steroidal anti-inflammatory (NSAI) agent.

64. The medication of Claim 62 wherein said second feedstock further comprises a non-steroidal anti-inflammatory (NSAI) agent.

INTERNATIONAL SEARCH REPORT

US 2/10978

CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 9/10, 9/14, 9/02, 9/22
US CL : 424/434, 435, 484, 489, 465

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/434, 435, 484, 489, 465, 78.38, 426, 485, 488, 499, 500;
514/925-928, 960

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 3,762,846 (CHIVERS) 02 OCTOBER 1973 See column 3, lines 39-51.	1-11,15-32 36-55,59-64
X	US, A, 4,885,281 (HANSTEIN) 05 DECEMBER 1989 See column 2, lines 25-29; column 3, lines 41-46.	1-11,15-32 36-55,59-62
X	US, A, 4,855,326 (FUISZ) 08 AUGUST 1989 Abstract; column 9, Table V; column 11, line 41; column 4, lines 40-44.	1-11,15-32, 36-55,59-62

☐ Further documents are listed in the continuation of Box C.

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Date of the actual completion of the international search
16 FEBRUARY 1993

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